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STEVEN L. HIGHLANDER
FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVENUE, SUITE 2400
AUSTIN, TX 78701

EXAMINER	
SALIMI, ALI REZA	

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RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SHUYUAN ZHANG

Appeal 2009-002156
Application 09/203,078
Technology Center 3600

Oral Hearing Held: July 21, 2009

Before FRANCISCO C. PRATS, MELANIE L. MCCOLLUM, and JEFFREY N. FREDMAN, *Administrative Patent Judges.*

APPEARANCES:

ON BEHALF OF THE APPELLANT:

GINA N. SHISHIMA, ESQUIRE
Fulbright & Jaworski, LLP
600 Congress Avenue
Suite 2400
Austin, Texas 78701-2978
(512) 474-5201

The above-entitled matter came on for hearing on Tuesday, July 21, 2009, commencing at 10:05 a.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia, before Dawn A. Brown, Notary Public.

P R O C E E D I N G S

THE USHER: Calendar number 35, appeal number 2009-2156. Ms. Shishima.

JUDGE PRATS: Good morning.

MS. SHISHIMA: Good morning.

JUDGE PRATS: Whenever you're ready, you have 20 minutes. Thank you.

MS. SHISHIMA: Thank you. May it please the Board. I'm Gina Shishima from Fulbright & Jaworski representing the Applicants in this case.

I think this case involves two main issues, one of anticipation involving inherency, the second one is obviousness under 103 based on the same reference in the 102 inherent anticipation as well as a combination of other references. I think on the inherent anticipation it is clear the reference, and I believe it -- I call it Huyghe, et al. I'm not sure if that is the right pronunciation. But, of course, nowhere anywhere in the reference does it talk about the second step which is infecting producer cells in culture with adenovirus or the producer cells are infected through mid-log phase of growth and stationary phase of growth.

JUDGE FREDMAN: What is mid-log phase? In other words, how broad a time period is that in your view?

MS. SHISHIMA: I think if you look at the one example or -- I'm sorry, the one reference that we showed, Kuchler, which does provide a pictograph, so if you let me turn this way. If you imagine an exponential stage of growth, it would be the midpoint of that where it starts to ramp up,

then it goes up. That would be the midpoint between there and where it hits the plateau.

JUDGE FREDMAN: Right. But I mean, if Huyghe, I'll use the reference as an example, yours is little bit of a shorter time period, at least based on some of the claims, it takes two-and-a-half days to reach 60 percent confluency and then they infect and then a few days later they harvest. If they had not infected, right, it would have continued presumably to grow, how long -- how many minutes, hours, days is the period of mid-log phase?

MS. SHISHIMA: I think that is the problem with the Huyghe reference, is you can't tell because there is not enough information. And so for a reference under inherent anticipation, it has got to be more than mere possibilities and probabilities.

And so what we provided was some information about – so there is a lag phase. So when I talked about the curve and the curve goes like, and that is because cells in the initial stage have to get adjusted and they don't start growing.

And so the thing is, the Kuchler reference which shows that pictograph was used to show that it can take, I think, it was 24 to 48 hours to get out of lag phase. And so for talking on that, at least on the one hand, the 48 hours, then those cells were only in the growing phase for 12 hours. And under that, I think that would not be at least mid-log phase of growth, which is what the claims require.

JUDGE PRATS: It seems like, though, the Examiner picked this because 1404 Huyghe talks about you're at 50- to 60-percent confluency, and so we're basically using confluency as an indication of where you are,

you know, in the overall growth. So I mean, why isn't that -- why is that wrong?

MS. SHISHIMA: Because you can imagine -- I mean, confluency is just how packed the cells are. That doesn't in the end say or indicate what phase of growth the cells are in. For example, and I'll just cut to the chase to one of the references, it talks about a higher percentage of confluency.

You can imagine they actually pulled five plates together to get to that level of competency. I think with Huyghe, the Examiner there was more thought put into it because it did say 2 to 2.5 days later it reached 50- to 60-percent confluency. But I think as far as establishing whether that is at the midpoint of growth, that just hasn't been done in this case.

That hasn't been shown by the Examiner. I can't tell; the Examiner can't tell. All we can show is that it is probably not the case and that is with some assumptions --

JUDGE FREDMAN: You could actually try to demonstrate it was impossible.

MS. SHISHIMA: Yeah. And I think what we showed -- what our expert did was pick a density that was reasonable and showed that, in fact, it would be 12 hours or --

JUDGE FREDMAN: With your experts, it didn't quite seem clear to me. Because in the -- I don't know the name of your expert.

MS. SHISHIMA: Gallagher.

JUDGE FREDMAN: Gallagher. Thank you. In Gallagher's declaration, the assumption was that there would be a short lag phase and

then a 36-hour growth period, which is about one doubled. If we're doubled 50- to 60-percent confluency, that essentially when we're doubling takes us up to 100-percent confluency, right, which is essentially stationary phase.

So we're essentially -- by your expert's declaration, we're kind of at the midpoint between the first doubling and a second doubling, which is then going to fill this chamber.

MS. SHISHIMA: One, I don't know if confluency if the cell is spread out, I just don't know whether, in fact, it is true the statement that one more doubling puts you at 100 percent. I somewhat doubt that in some ways because if you look at our own specification, we talk about infecting eight days post-infection.

JUDGE FREDMAN: That is deep into stationary phase, right? In other words, you double then you actually hit stationary phase at which point there is very little additional growth.

MS. SHISHIMA: Well, I guess the thing is in the end, we don't know what the density is. So your point is, if we were at 50 to 60 percent, it would have taken one more doubling and we would have been beyond.

JUDGE FREDMAN: Well, we would have been around stationary phase. You know, so the question is, based on your expert's actual declaration, unfortunately the reasonable position is, I think that we're very close to, if not in, mid-log phase.

MS. SHISHIMA: And I think the point of the expert declaration was to try to not take the extremes and just --

JUDGE FREDMAN: No, no, no. And I appreciate that. I think that was appropriate to do.

MS. SHISHIMA: I certainly think the expert 's declaration makes it possible that, sure, after one more day they would have gotten there but they didn't get there.

JUDGE FREDMAN: One more day they would have been clearly at stationary phase. That is way past where they needed to be. They needed to be at mid-log to meet the claim. They had to be somewhere at mid-log now, whatever that is.

MS. SHISHIMA: So I thought that we had provided information that the doubling was around 30 to 36 hours.

JUDGE FREDMAN: Right. Uh-huh.

MS. SHISHIMA: So if we go 12 hours and we're at 50 to 60 percent to get to somewhere halfway, we'd at least need to get to at least another -- I don't know, half of 30 to 36 or somewhere between 15 and 18.

JUDGE FREDMAN: But if we're at 60-percent confluency, which is what we know we're at, and if you say the growth -- I'm just reading from the declaration -- the initial density is a certain density, midpoint of the assumption range. The growth period is 2.5 days minus lag time, so 1.5 days, which is 36 hours, so with the doubling time of 36 hours, the cell population will double once.

So essentially they're saying -- they say that that is really a log-phase density. But in fact, we know the confluence is 50 to 60 percent, and we know that they have one doubling, essentially, according to this declaration to get to this. So presumably it started off at 25-percent confluency or something like that. So the next doubling should take us to 100-percent confluency.

MS. SHISHIMA: I just don't know if that is the way that that works when you look at confluency, if the cells don't pile up on each other more or not. I just don't know.

JUDGE FREDMAN: Two out of three cells.

JUDGE PRATS: The other argument seems to be if you seeded really high density, you get -- presumably seed it 50/60 percent, correct, and then you would still be in the stage 4 phase at that?

MS. SHISHIMA: No, actually it would be the opposite.

JUDGE FREDMAN: You mean lag phase.

JUDGE PRATS: Lag. That is what I mean to say. Sorry.

MS. SHISHIMA: Right. Which is --

JUDGE FREDMAN: But we know that they probably couldn'thave seeded that high because it is two-and-a-half days after they started. So after two-and-a-half days, they wouldn't still be in lag phase. So that is not reasonable really.

JUDGE PRATS: Okay.

MS. SHISHIMA: But I think in the end this is one of, like I said, at least -- first we'll talk about inherent anticipation. Of course, that segues into the obviousness argument.

From an inherent anticipation legal standard, I think that either we could argue that the Examiner has not even met the burden to show they provided a reasonable basis that the limitations of the claim were met, or to the extent that it has, we have provided information that were in the realm of possibilities and probabilities, which is not where we need to be from the standpoint of inherent anticipation.

Now, we can talk about the obviousness issue. So the question is, if you're still in a situation where you just don't know, you don't know where Huyghe is. You don't know if Huyghe is talking about mid-log phase of cell growth to stationary phase of cell growth. I think it is pretty safe to say it is not at stationary phase.

JUDGE FREDMAN: The other concern, though, I mean, I guess, and this is just the way your claims are set up, this claim 8, and this is sort of bringing us back to the inherent anticipation as evidentiary information. Claim 8 says they were seeded into the cultural medium, allowed to attach for 3 hours to about 24 hours prior to infection.

The implication then is that when you do that, that that is sufficient to get you to mid-log phase, right, because it has to be -- presumably incorporates all of claim 1 and, therefore, has to be properly dependent.

Now, we know from Huyghe that he did that for a longer period or that he did that for, in fact, 48 hours or 60 hours, something like that, so that he seeded and allowed them to attach for a much longer period and yet with the same cell type. And so with the same cell type, we're achieving the same result. That tends to support the Examiner's case at least based on justclaim interpretation.

MS. SHISHIMA: I'm not understanding. So --

JUDGE FREDMAN: Your claim 8 says that we take cells and we seed them into their culture medium and let them sit for 3 to 24 hours prior to infection. So if we incorporate that into claim 1, that means that we prepare the producer cells then -- in preparing them, what that means is that they are in mid-log phase because that is a requirement of claim 1. So that

means that at least according to claim 8, 3 to 24 hours is sufficient at least in some instances to get us to mid-log phase.

MS. SHISHIMA: I guess I'm not seeing why the attachment part has anything to do with what phase of growth they're in. I mean, you can imagine that they just sit there and they're attaching for those first 3 to 24 hours.

JUDGE FREDMAN: But then you have infection without virus. That seems to be the next step.

MS. SHISHIMA: Right. But it is still --

JUDGE FREDMAN: The implication is that the next thing you do after 24 hours or whatever is you infect.

MS. SHISHIMA: I'm not sure why there couldn't still be at least another -- it just says between and about you allow them to attach. I think -- I don't see why it has to be the case that you have to then infect within -- or right after 24 hours and 1 minute. But --

JUDGE FREDMAN: Okay.

MS. SHISHIMA: If I understand.

JUDGE FREDMAN: Yeah. I think you understand me. I see your point.

MS. SHISHIMA: So if we talk about the 103 issue -- okay. Like I said, we don't really know where Huyghe stands as far as what phase. I hink if we look at any of the other references with the exception of one, the other ones are also silent on what phase of cell growth the cells are at when they may or may not be infected.

If we first talk about Huyghe itself as an obviousness reference, I don't really think we're any farther along than where we were on the 102. We just don't know. And I think it just does not then establish an element of the claim, which is step 2.

When you combine it with the other references, there is a Huyghe and Graham combination, and in the end, Graham is relied upon to teach the lysing aspect of these claims. The Examiner doesn't rely upon it for anything else other than that.

If you talk about Huyghe, Graham and Lew, and the Lew reference is relied upon to teach the element of infection at late log phase of growth. I think our Briefs talk about how Lew is about hepatitis A virus. It does have a list of viruses. We go through the differences between hepatitis A virus and adenovirus. There are a significant number.

And then an Examiner came back and said, well, in that list of viruses and in addition to hepatitis A, there are some that have more similarities maybe to adenovirus, for example, being double-stranded DNA viruses.

In the end, though, if you look at the Lew reference, it talks a lot about how -- and I'll just point you to column 5. It says, "The method is applicable to production of other viruses where virus productivity can be enhanced by creating a stable culture during an extended infection period."

And if you look in other paragraphs or in other columns, it goes on to say that the hepatitis A virus and the MRC-5 cells that they use on the glass-coated micro-carriers are -- they exemplify the process of the invention, and it says how the invention is particularly significant for slow-growing viruses such as hepatitis A virus.

And it then goes on to say -- it talks about slow-growing viruses, and it says, "In the case of HAV and MRC-5 culture, the cell population must remain stable over a course of a 21-day infection process." That is, I think, significantly different than the adenovirus process we're talking about.

So in our protocol that we show in figure 28, we talk about an eight-day post-infection. And I think among the references it talks about how there is just no more cells alive.

JUDGE FREDMAN: And your eight-day post-infection is really just your infected stationary phase. It is something you're infecting for eight days.

MS. SHISHIMA: No, that is correct. You infect for eight days, but I think there are references that show that -- we actually then harvest at day 5 after that. So not 21 days. And so most cells are going to be dead, I think, around day 6 is what one of the references talked about.

And in part, it is because, and this goes to one of the differences we pointed out, adenovirus is a lytic virus, HAV is not a lytic virus, so lytic viruses infect the cell, replicate, then burst open the cell. No more cells to infect. They're dead.

So I think the point is that the Lew reference, which is the only one which makes any mention of what phase of growth that cells are in, is pertaining to a different kind of virus.

JUDGE FREDMAN: I'm not a hundred-percent sure that the Examiner is -- I guess he argues it.

MS. SHISHIMA: He argues it as a dependent limitation.

JUDGE FREDMAN: Right. He doesn't really argue it for the dependent claims. He doesn't actually push it back to the independent claims for some reason.

MS. SHISHIMA: I agree. I agree with your assessment of what the Examiner did.

And I think the thing is Lew goes so far as to even say the length of time provided for cell growth is, quote, not critical, in column 11. So if you thought maybe I'll look at Lew. It talks about a different virus, but I'll look at it. It says it is not critical in column 11.

So I think over all what you're left with -- sorry -- at least with respect to the Huyghe, Graham and Lew combination, is it doesn't add up to one of ordinary skill in the art turning to these references to produce the claimed invention, certainly not with any reasonable expectation of success or with predictability as required under 103.

The other obviousness rejection is Huyghe, Garnier and Spear. Garnier -- so Huyghe doesn't say anything about what phase of cell growth. Garnier is about protein production, and we made an argument about why protein production and virus production are different. The Examiner said that virus production was mentioned in the abstract.

But I'll point out that Garnier itself says on page 151cell growth culture stage does not influence protein production since cells infected and the culture produced as much protein as one-day-old infected culture. And I think, again, it doesn't say anything about why you would go to this other phase of cell growth.

Spear is about viral reactors and aspects of scaling up. It has a conclusion that says reactors should not be thought of in isolation because it does talk about different viral reactors. It says probably the biggest increases in productivity will come as a result of studying self-physiology in more depth and from development, i.e., it is acknowledging other areas in which development can occur.

It says, "In conclusion, the idea of large volume-dense culture system is tantalizingly close but needs technical developments in several related areas to bring it about." And it ends right there. Doesn't provide guidance as to where that may come from. It doesn't say anything about the phase of cell growth.

I think just over all, all we're left with is no reference says anything about phase of cell growth being related to virus production. Certainly not adenovirus production. Or actually any other virus production for that matter.

And so I submit that the Examiner in this case has not met the burden under 102 or under section 103.

JUDGE MCCOLLUM: I don't have any questions.

JUDGE PRATS: Questions?

JUDGE FREDMAN: No more.

JUDGE PRATS: Anything further?

MS. SHISHIMA: I think that is it. Thank you.

JUDGE PRATS: Thank you very much.

MS. SHISHIMA: One more thing I want to say on the record. We do have other dependent claims that are separately patentable and I didn't argue them, of course.

JUDGE PRATS: Thank you.

(Whereupon, the proceedings at 10:25 a.m. were concluded.)